Polydynamic Biological Activity of Quercetin

Subjects: Chemistry, Medicinal

Contributor: Nikitas Georgiou , Margarita Georgia Kakava , Efthymios Alexandros Routsi , Errikos Petsas , Nikolaos Stavridis , Christoforos Freris , Nikoletta Zoupanou , Kalliopi Moschovou , Sofia Kiriakidi , Thomas Mavromoustakos

Quercetin is one of those natural products. It belongs to the family of flavonoids and, more specifically, flavonols. Quercetin is an organic compound that belongs to the family of flavonoids, with a wide range of medical properties. Some of these include anti-allergy, anti-inflammatory, anticancer, anti-tumor, and antiviral properties as well as cardiovascular protection. It has also been found that quercetin plays a vital role in plants. Specifically, quercetin has antioxidant and antimicrobial activities, and as a result, it contributes to photosynthesis, growth, and seed germination. Moreover, the presence of quercetin in various regions of the brain contributes to combatting against various neurological diseases such as Alzheimer's and Parkinson's.

quercetin flavonoids

1. Mental Activity

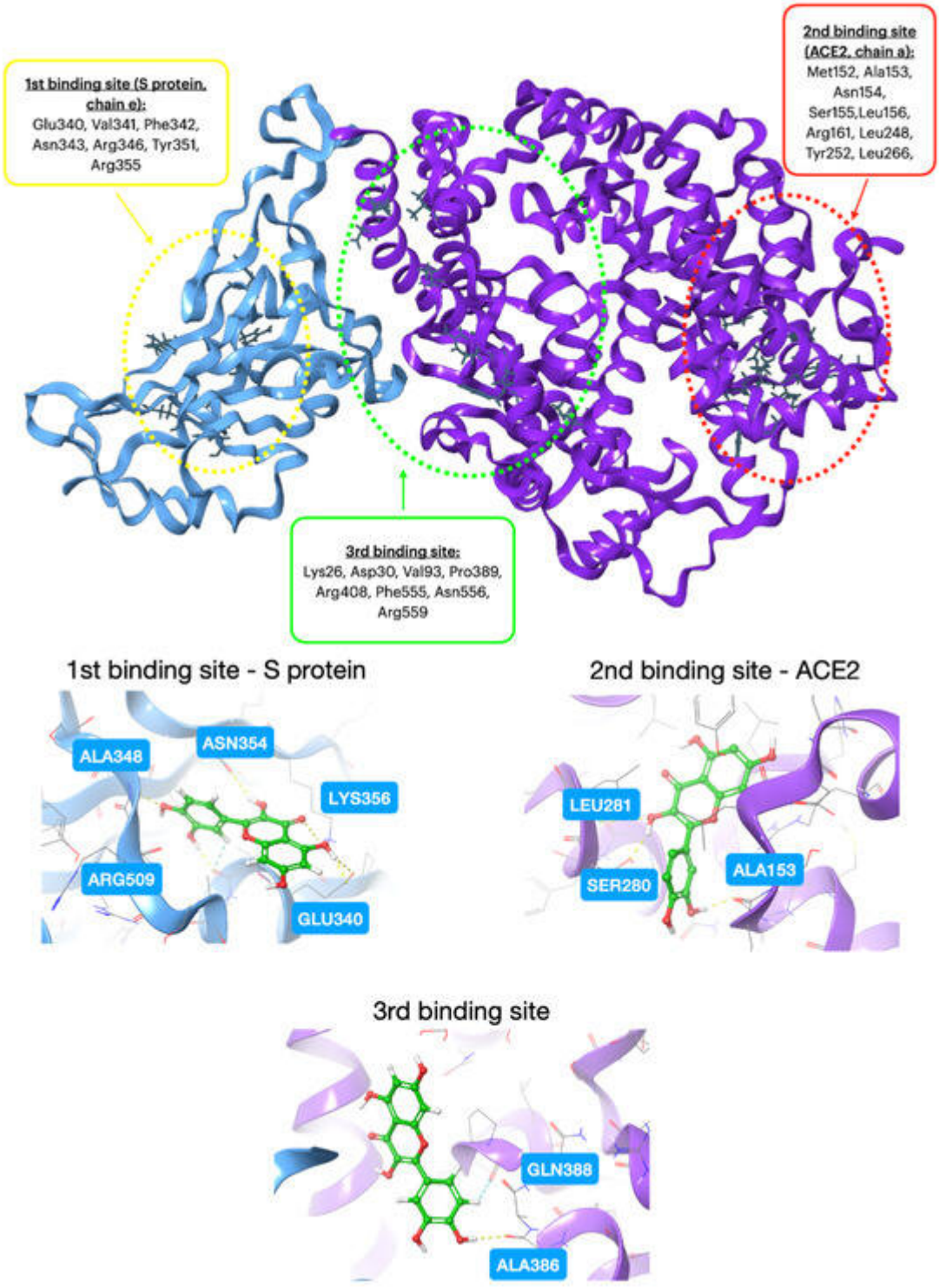
Quercetin can play a significant role in mental health diseases [1] such as depression and anxiety. Mice studies have demonstrated that some natural products including quercetin possess anxiolytic properties when administered orally. Moreover, they are unlikely to have side effects serious enough to prevent their pharmacological utility, so they could constitute the starting point for the development of more selective anxiolytic agents [2]. Due to its antioxidant activity, quercetin can lower nitric oxide and some other compounds that are vital for these diseases. According to SwissADME, quercetin can inhibit CYP isoenzymes. As a result, it can protect the organism from pathogenic factors.

2. Ultraviolet (UV) Activity

One study has shown that quercetin encapsuled with polymer nanoparticles can be efficient for sun protection [3]. In recent years, ultraviolet (UV) radiation has been considered a public threat for health worldwide, as it is responsible for acute and chronic skin diseases, such as burns, premature aging skin, and carcinogenesis. Skin cancer is the most common type of cancer that is diagnosed worldwide. It can cause a high degree of mortality when it develops into its most severe form, that of melanoma. Thus, necessary protection is required during exposure to sunlight. Today, sunscreens are used to protect us from early photoaging, photosensitivity, skin cancer, and free radical damage. The main goal of sunscreens is to protect the human skin from UVA and UVB radiation. Recent studies have shown that compounds from natural plants may act as sun protectors [4]. Quercetin is one of those natural products that can reduce the damage from UV radiation.

3. Antiviral Activity

Viral diseases are still a problem even after the discovery and use of antiviral drugs for more than 60 years now, due to the toxicity of some new antiviral preparations and the development of resistant viral strains. The human immunodeficiency virus (HIV) [5] is another disease that started to spread throughout the world. HIV has two categories, HIV type 1 and HIV type 2 (HIV-2). HIV was first recognized in 1981 in the USA. The origin of this virus is primate lentiviruses, which exist in chimpanzees. These animals became the host of the virus, which is then transmitted to humans after mutations [6]. Quercetin and isoquercetin have antiviral activities against many types of viruses, including human immunodeficiency virus. Many scientists have suggested quercetin as an antiviral drug due to the fact that it can inhibit the first stages of the virus infection. Quercetin has also been found to exert important pharmacological activity against several other viruses [7]. One such activity is against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [8][9], which recently emerged as a global threat to human health. It is the main cause of the COVID-19 pandemic that caused more than 6,000,000 deaths worldwide. Quercetin has been found to be able to interfere with SARS-CoV-2 and reduce the inflammation provoked by COVID-19 (**Scheme 1**). Also, blood tests have indicated that quercetin can reduce the time during which the molecular test appears positive by reducing the viral charge [10].



Scheme 1. Three-dimensional (3D) structure of spike protein bound to ACE2 (PDB ID: 6M0J). The dotted circle identifies the amino acids that constitute the respective binding sites for the Induced Fit Docking (IFD) experiments (**above**). The interactions were developed from the IFD experiments for quercetin with spike proteins of SARS-CoV-2 from the three studied binding sites (**bottom**). This image was sketched using Maestro software Version 10.2.

4. Anticancer Activity

Cancer is a serious disease that hurts many developed and developing countries. There are more than 100 types of cancer. Most often, a specific type of cancer is characterized by the type of cell in which it is formed. The most basic types of cancer are carcinoma, sarcoma, leukemia, lymphoma, multiple myeloma, melanoma, and brain and spinal cord tumors [11].

Quercetin has been found through in vitro experiments to exhibit anti-tumor activity against prostate [12][13], liver [14], breast [15], and pancreatic [16] cancer and melanoma [17]. Quercetin's anticancer effects on hepatocellular carcinoma [18] have been studied not only in vitro but also in vivo. Although the exact mechanism of action remains elusive, quercetin's anticancer effect may arise by regulating some enzymatic activities or also by modulating oxidative stress and some cellular pathways.

Chemoprevention involves treating cancer before it becomes aggressive, but it does have its downsides. This approach can potentially lead to side effects and toxicity. Quercetin has demonstrated synergistic effects in addressing tumors with multidrug resistance by blocking the expulsion of drugs facilitated by transporter proteins. It is used as a low-toxicity medicine. Studies have shown that the anticancer activity of quercetin can be improved by encapsulating quercetin inside nanoparticles. In vitro and in vivo studies have shown successful tumor treatment using quercetin nano-formulations. These approaches can reduce side effects. Some examples include polymeric nanoparticles, non-responsive polymeric nanoparticles, and stimuli-responsive polymeric nanoparticles. There are also examples of inorganic nanoparticles with quercetin—specifically, silica nanoparticles, gold nanoparticles, and metal oxide nanoparticles [19].

5. Anti-Inflammatory Activity

Moreover, quercetin has been shown to exert anti-inflammatory activity. Inflammation is a multifactorial and complex biological response of body tissues to harmful stimuli, so as to restore the organism to homeostatic balance. Inflammation is found in some areas of the body and refers to the tissues of an organ or a tissue or a whole organ, etc. (e.g., arthritis, tendonitis, stomatitis, peritonitis, etc.). Rheumatoid arthritis is an example of an autoimmune inflammatory disease [20]. This disease affects more women than men, and it was discovered many years ago. The symptoms of this disease are stiffness and swelling that appear in the feet, fingers, and toes. In vitro [21] studies have shown that quercetin may be a good drug candidate for the treatment of this disease, because it can inhibit neutrophil activity. It can also inhibit the activation of NLRP3 inflammasomes [8]. Lipoxygenases (LOXs) are a group of monomeric oxidant metalloproteins, containing a non-heme-coordinated iron atom (non-heme ion Fe) [22][23]. Moreover, several in vitro experiments have shown that quercetin can inhibit soybean lipoxygenase [24], which is involved in inflammation.

6. Neurological Activity

Alzheimer's disease (AD) [25] is a fatal complex neurodegenerative disease that affects more than 24 million people worldwide [26]. The disease is characterized by multiple pathological features and is clinically associated with

cognitive impairment, language loss capacity, and dementia. Current treatment options include results with moderate improvement of memory and cognitive function; however, they do not prevent progressive neurodegeneration. Multifunctional compounds capable of simultaneously interacting with the ingredients of many pathologies have been considered as a solution and are being researched for the treatment of complex pathologies of neurodegenerative diseases [27][28]. Quercetin is one of these compounds that can be used against Alzheimer's disease due to the fact that it has a neuroprotective effect against oxidative stress [29].

7. Antioxidant Activity

When found in moderate concentrations, the active forms of oxygen (reactive oxygen species, ROS) participate in the normal processes of the organism, but their production in large concentrations leads to oxidative stress, disrupting the organism's cellular oxidation balance [30][30][31]. Antioxidants are substances that can protect cells against oxidation and the effects of free radicals, because they annihilate these radicals from the medium. They also constrain oxidation by oxidizing themselves. Antioxidants suppress various harmful activities of ROS, so they are used to prevent or treat such diseases. One health problem that oxidative stress is associated with is obesity. Obesity is one of the major health problems in the world, and it leads to increased amounts of fat cells. It is characterized by the overproduction of reactive oxygen stress. Quercetin, along with other natural products, has been shown to exert beneficial effects against obesity through different molecular pathways. In vivo experiments using obese rats have been shown to lose weight after treating with quercetin [32].

Moreover, Jose Angel Maranon Maroto proved that a combination of the polyphenols resveratrol, quercetin, and catechin has synergic antioxidant power. Polyphenolic compounds of natural origin are recognized as antioxidant agents, which act as free radical scavengers. Resveratrol is a polyphenolic compound that is present mostly in seeds and in the skin of grapes and other plant products [33].

8. Anti-Cardiovascular Disease

Heart diseases or cardiovascular diseases are those diseases that involve the heart or blood vessels (arteries and veins) [34]. Though the term technically it refers to any disease affecting the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial diseases). These diseases present similar causes, mechanisms, and treatments. Most countries face high and increasing rates of cardiovascular diseases. It has been shown that they affect adolescents and kids, and for this reason, prevention against them is mandatory from childhood. When heart problems are diagnosed, the underlying cause (atherosclerosis) is usually quite advanced. Therefore, more emphasis is placed on the prevention of atherosclerosis through the modification of risk factors, such as healthy eating, exercise, and avoiding smoking. The protective effects of quercetin against cardiovascular diseases include the reduction of blood pressure and arterial pressure. Hypertension is the most common cause of cardiovascular diseases, such as in cardiac hypertrophy, responsible for abnormal cardiac growth, which leads to arrhythmia, myocardial infraction, and heart failure [35]. Many people currently suffer from hypertension, an alerting sign that pharmacological and natural interventions are needed in order to decrease blood pressure and inhibit

various biochemical pathways that are involved in cardiovascular diseases. Studies have demonstrated that quercetin can decrease blood pressure via multiple mechanisms like inhibiting protein kinase C (PKC), a family of protein kinase enzymes implicated in governing heart failure [36], decreasing oxidative stress, inhibiting angiotensin, converting enzyme activity, or even modulating cell signaling and gene expression [37].

9. Skin Sensitivity

Numerous individuals experience skin wounds, which can be either chronic or temporary and may affect a substantial area of the skin. Healing processes typically fall into three categories: primary healing (also known as healing by first intention), which takes place within 12 to 24 h after the wound forms; secondary healing (or healing by second intention), observed in wounds with significant loss of soft tissue; and the healing of superficial wounds, such as those seen in superficial burns and abrasions, involving the epithelium and the papillary part of the dermis. Natural products, especially those from plants, are a new strategy for wound healing. Quercetin is used for the treatment for wounds because, as outlined, it shows anti-inflammatory activity. *Rubusniveus* [38] is one of the species against which quercetin was found to have some wound-healing activity [39].

There are a lot of examples of the biological activity of quercetin occurring in in vivo experiments. One example is in the species of *Bergia ammannioides* [40], against which quercetin was found to have antioxidant and anti-inflammatory abilities. Secondly, in *Melilotus officinalis* and in *Lespedeza capitata* [41], quercetin was found to increase the HaCaT human keratinocytes. Furthermore, in *Martynia annua* and *Tephrosia purpurea* [42], quercetin was found to have antioxidant activity. Also, quercetin has protection against endotoxin-induced inflammatory response [43], surgical-induced osteoarthritis [44], LPS-induced oxidative stress and inflammation [45], LPS/interferon c-induced nitric oxide production [46], TNF-α induced inflammation [47], and CCl4-induced inflammation [48].

10. Anti-Tuberculosis

Tuberculosis is a fatal infectious disease caused by the Mycobacterium tuberculosis (*Mycobacterium tuberculosis*). Despite the availability of effective treatment, tuberculosis is responsible for a million deaths worldwide per year. The bacterium has developed a resistance to the drugs on the market, and so the need arises to find other therapeutic compounds [49][50]. Quercetin can be a good inhibitor for the bacterium [51]. This was found through in vitro antituberculosis bioassays.

11. Antidiabetic Activity

Insulin is a protein hormone that is necessary for the maintenance of normal blood glucose levels, either by increasing peripheral glucose uptake or by suppressing the production of hepatic glucose [52]. Quercetin might be a promising candidate that acts in many targets of diabetes, and it can regulate many pathways [53][54]. Furthermore, co-crystals comprised of quercetin and antidiabetic agents like metformin and DPP-IV inhibitors have been demonstrated to treat diabetes mellitus (DM) by reducing blood glucose levels and improving glucose tolerance.

DM is a chronic disease that is diagnosed as a result of elevated blood glucose levels caused by inadequate insulin secretion, defective insulin action, or both [55][56].

12. Antimalaria Activity

Malaria is one of the most threatening tropical diseases that leads to millions of deaths every year. Almost all fatal cases are caused by *Plasmodium falciparum* and its strains, which have developed resistance to the drugs in circulation. Therefore, a need has arisen for new active compounds for the treatment of this disease. Quercetin is a potential antimalaria drug, as proven through in vitro experiments [57].

13. Antichagas Activity

Chagas disease (CD) [58] is a disease that many scientists ignore, and its main bacteria is the *Trypanosoma cruzi* (TC). This disease appears mainly in Central and North America, but in recent decades, the number of CD cases has been increasing in other countries, such as in the south of the United States of America, in Canada, in the Western Mediterranean, and in the Western Pacific. It is estimated that about 6 to 7 million people are potentially infected by TC, which causes about 20,000 deaths per year and is the leading cause of infectious myocarditis. Quercetin and other flavonol derivatives can be antitrypanosomal candidates, showing IC_{50}s of 0.6, 0.7, 0.8, and 1.0 µg/mL [59].

14. Antifungal Activity

Fungicides have often been observed to pose a risk to human health and can be harmful to the environment. Thus, there is a need to find alternative solutions to deal with fungi, with natural compounds that will not affect either human health or the environment. The *Candida parapsilosis* species is composed of three other species, i.e., *C. parapsilosis sensu lato*, *C. orthopsilosis,* and *C. metapsilosis.* These species are found in vegetables and fruits, and they are known to cause infections worldwide. Quercetin has been shown to have antifungal activities through the determination of its minimum inhibitory concentration (MIC) [60].

15. Combination of Quercetin with Other Drugs

There are several examples whereby quercetin and its derivatives have been combined with other compounds with biological interest and activity. One of these examples is sickle cell disease. Sickle cell disease and its variants constitute the most common blood disorders, affecting millions of individuals worldwide. Until now, there has been no treatment for this disease, and there is no acute method for prevention [61]. Another example is Fragile X Syndrome. This disease is the most common one implicated in intellectual disability. Someone who suffers from this disease has many serious medical problems [62].

16. Anti-Rhinitis Activity

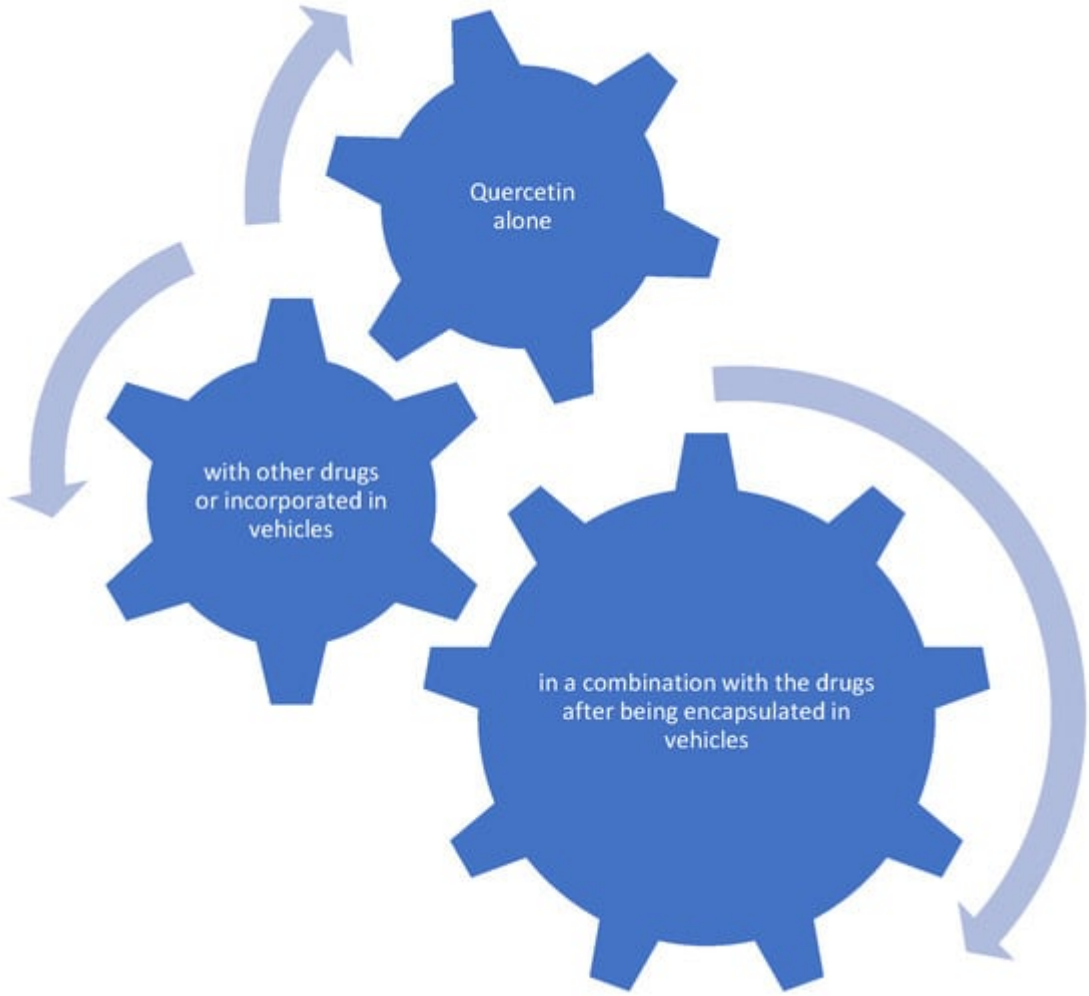
Acute rhinitis is one of the most common inflammatory diseases in Western countries. The major symptoms include nasal obstruction and nasal secretions. In the evolution of the disease, a frequent complication is acute rhinosinusitis, which can progress to chronic rhinosinusitis and then to intracranial complications, meaning that it is necessary to treat the disease as soon as possible. The cause of rhinosinusitis lies in the secretion of pro-inflammatory cytokines, key factors in initiating inflammation, consequently leading to local edema and swelling of the mucosa and an increase in nasal and sinus secretions. Quercetin has proven its antioxidant and anti-inflammatory properties against rhinosinusitis, both in rats and humans, by inhibiting the release of chemical mediators, such as histamines and leukotrienes, and reacting with relative oxygen species (ROS), which are also involved in rhinosinusitis [63][64].

17. Antidrug Resistance

Multidrug resistance (MDR) is defined as the ability of cancer cells to survive treatment with a variety of anticancer drugs, similar to the concept commonly applied to antibiotic treatment [65]. MDR is responsible for over 90% of deaths in cancer patients receiving chemotherapeutics or targeted drugs. Derivatives of quercetin have been proven to be possible candidates in treating MDR cancer, as well as viral infections in humans [66].

Skeletal muscles are tissues that are involved not only in mobility and movement but also in glucose and lipid metabolism. Muscle atrophy is the loss of skeletal muscle mass due to increased myofibrillar protein degradation. It occurs under various circumstances such as injury and during side effects of pharmaceutical therapy and aging. Muscle atrophy causes falls, and therefore, it has become a serious problem, especially in aging society. Quercetin glucosides are proven to be perfect candidates in the treatment of muscle atrophy, since they play an important role in the downregulation of myostatin signaling via phosphorylation, a possible mechanism responsible for the inhibitory effects of quercetin glucosides [67][68].

All in all, quercetin is commercially available and is one of the most common natural products. Natural products have become more popular, and they have started to be used as lead compounds in medicine. They have a lot of advantages in contrast to common drugs. For instance, they have less side effects. In addition, flavonoids play a significant role in humans and plants. Efforts that have been made to increase the bioavailability and solubility of quercetin are outlined in the Results and Discussion section. Basically, vehicles have been used, and quercetin is also administered with other drugs (**scheme 2**).



Scheme 2. Quercetin alone bears low bioavailability and solubility. In an attempt to increase both its bioavailability and solubility, it was encapsulated in vehicles using nanotechnology. In addition, it is administered with other drugs.

References

1. Hosseini, A.; Razavi, B.M.; Banach, M.; Hosseinzadeh, H. Quercetin and Metabolic Syndrome: A Review. Phyther. Res. 2021, 35, 5352–5364.
2. Yoon, B.H.; Jung, J.W.; Lee, J.-J.; Cho, Y.-W.; Jang, C.-G.; Jin, C.; Oh, T.H.; Ryu, J.H. Anxiolytic-like Effects of Sinapic Acid in Mice. Life Sci. 2007, 81, 234–240.
3. Nunes, A.R.; Vieira, Í.G.P.; Queiroz, D.B.; Leal, A.L.A.B.; Maia Morais, S.; Muniz, D.F.; Calixto-Junior, J.T.; Coutinho, H.D.M. Use of Flavonoids and Cinnamates, the Main Photoprotectors with Natural Origin. Adv. Pharmacol. Sci. 2018, 2018, 5341487.
4. Fogaça, L.A.; Feuser, P.E.; Ricci-Júnior, E.; Hermes de Araújo, P.H.; Sayer, C.; da Costa, C. ZnO and Quercetin Encapsulated Nanoparticles for Sun Protection Obtained by Miniemulsion

Polymerization Using Alternative Co-Stabilizers. Mater. Res. Express 2020, 7, 015096.

5. Reeves, J.D.; Doms, R.W. Human Immunodeficiency Virus Type 2. J. Gen. Virol. 2002, 83, 1253–1265.
6. Sharp, P.M.; Hahn, B.H. The Evolution of HIV-1 and the Origin of AIDS. Philos. Trans. R. Soc. B Biol. Sci. 2010, 365, 2487–2494.
7. Di Petrillo, A.; Orrù, G.; Fais, A.; Fantini, M.C. Quercetin and Its Derivates as Antiviral Potentials: A Comprehensive Review. Phyther. Res. 2022, 36, 266–278.
8. Wang, G.; Wang, Y.; Yao, L.; Gu, W.; Zhao, S.; Shen, Z.; Lin, Z.; Liu, W.; Yan, T. Pharmacological Activity of Quercetin: An Updated Review. Evid.-Based Complement. Altern. Med. 2022, 2022, 3997190.
9. Agrawal, P.K.; Agrawal, C.; Blunden, G. Quercetin: Antiviral Significance and Possible COVID-19 Integrative Considerations. Nat. Prod. Commun. 2020, 15, 1934578X20976293.
10. Moschovou, K.; Antoniou, M.; Chontzopoulou, E.; Papavasileiou, K.D.; Melagraki, G.; Afantitis, A.; Mavromoustakos, T. Exploring the Binding Effects of Natural Products and Antihypertensive Drugs on SARS-CoV-2: An In Silico Investigation of Main Protease and Spike Protein. Int. J. Mol. Sci. 2023, 24, 15894.
11. Oz, M.; Selcuk, I.; Arik, Z.; Gungor, T. Targeted Agents in Ovarian Carcinoma. Med. Sci. 2016, 5, 547.
12. Erdogan, S.; Turkekul, K.; Dibirdik, I.; Doganlar, O.; Doganlar, Z.B.; Bilir, A.; Oktem, G. Midkine Downregulation Increases the Efficacy of Quercetin on Prostate Cancer Stem Cell Survival and Migration through PI3K/AKT and MAPK/ERK Pathway. Biomed. Pharmacother. 2018, 107, 793–805.
13. Ward, A.B.; Mir, H.; Kapur, N.; Gales, D.N.; Carriere, P.P.; Singh, S. Quercetin Inhibits Prostate Cancer by Attenuating Cell Survival and Inhibiting Anti-Apoptotic Pathways. World J. Surg. Oncol. 2018, 16, 108.
14. Hisaka, T.; Sakai, H.; Sato, T.; Goto, Y.; Nomura, Y.; Fukutomi, S.; Fujita, F.; Mizobe, T.; Nakashima, O.; Tanigawa, M.; et al. Quercetin Suppresses Proliferation of Liver Cancer Cell Lines In Vitro. Anticancer Res. 2020, 40, 4695–4700.
15. Niazvand, F.; Orazizadeh, M.; Khorsandi, L.; Abbaspour, M.; Mansouri, E.; Khodadadi, A. Effects of Quercetin-Loaded Nanoparticles on MCF-7 Human Breast Cancer Cells. Medicina (B. Aires) 2019, 55, 114.
16. Pham, T.N.D.; Stempel, S.; Shields, M.A.; Spaulding, C.; Kumar, K.; Bentrem, D.J.; Matsangou, M.; Munshi, H.G. Quercetin Enhances the Anti-Tumor Effects of BET Inhibitors by Suppressing HnRNPA1. Int. J. Mol. Sci. 2019, 20, 4293.

17. Sturza, A.; Pavel, I.; Ancuța, S.; Danciu, C.; Dehelean, C.; Duicu, O.; Muntean, D. Quercetin Exerts an Inhibitory Effect on Cellular Bioenergetics of the B164A5 Murine Melanoma Cell Line. Mol. Cell. Biochem. 2018, 447, 103–109.
18. Wu, L.; Li, J.; Liu, T.; Li, S.; Feng, J.; Yu, Q.; Zhang, J.; Chen, J.; Zhou, Y.; Ji, J.; et al. Quercetin Shows Anti-tumor Effect in Hepatocellular Carcinoma LM3 Cells by Abrogating JAK2/STAT3 Signaling Pathway. Cancer Med. 2019, 8, 4806–4820.
19. Caro, C.; Pourmadadi, M.; Eshaghi, M.M.; Rahmani, E.; Shojaei, S.; Paiva-Santos, A.C.; Rahdar, A.; Behzadmehr, R.; García-Martín, M.L.; Díez-Pascual, A.M. Nanomaterials Loaded with Quercetin as an Advanced Tool for Cancer Treatment. J. Drug Deliv. Sci. Technol. 2022, 78, 103938.
20. Tanaka, Y. Inflammation and Regeneration Rheumatoid Arthritis. BioMed Cent. 2020, 40, 1–8.
21. Yuan, K.; Zhu, Q.; Lu, Q.; Jiang, H.; Zhu, M.; Li, X.; Huang, G.; Xu, A. Quercetin Alleviates Rheumatoid Arthritis by Inhibiting Neutrophil Inflammatory Activities. J. Nutr. Biochem. 2020, 84, 108454.
22. Chontzopoulou, E.; Papaemmanouil, C.D.; Chatziathanasiadou, M.V.; Kolokouris, D.; Kiriakidi, S.; Konstantinidi, A.; Gerogianni, I.; Tselios, T.; Kostakis, I.K.; Chrysina, E.D.; et al. Molecular Investigation of Artificial and Natural Sweeteners as Potential Anti-Inflammatory Agents. J. Biomol. Struct. Dyn. 2021, 40, 12608–12620.
23. Smirnova, E.O.; Egorova, A.M.; Lantsova, N.V.; Chechetkin, I.R.; Toporkova, Y.Y.; Grechkin, A.N. Recombinant Soybean Lipoxygenase 2 (GmLOX2) Acts Primarily as a ω 6 (S)-Lipoxygenase. Curr. Issues Mol. Biol. 2023, 2, 6283–6295.
24. Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, Inflammation and Immunity. Nutrients 2016, 8, 167.
25. Scheltens, P.; De Strooper, B.; Kivipelto, M.; Holstege, H.; Chételat, G.; Teunissen, C.E.; Cummings, J.; van der Flier, W.M. Alzheimer’s Disease. Lancet 2021, 397, 1577–1590.
26. Ruwizhi, N.; Aderibigbe, B.A. Cinnamic Acid Derivatives and Their Biological Efficacy. Int. J. Mol. Sci. 2020, 21, 5712.
27. Liao, Q.; Li, Q.; Zhao, Y.; Jiang, P.; Yan, Y.; Sun, H.; Liu, W.; Feng, F.; Qu, W. Design, Synthesis and Biological Evaluation of Novel Carboline-Cinnamic Acid Hybrids as Multifunctional Agents for Treatment of Alzheimer’s Disease. Bioorg. Chem. 2020, 99, 103844.
28. Lan, J.S.; Hou, J.W.; Liu, Y.; Ding, Y.; Zhang, Y.; Li, L.; Zhang, T. Design, Synthesis and Evaluation of Novel Cinnamic Acid Derivatives Bearing N-Benzyl Pyridinium Moiety as Multifunctional Cholinesterase Inhibitors for Alzheimer’s Disease. J. Enzym. Inhib. Med. Chem. 2017, 32, 776–788.

29. Salehi, B.; Machin, L.; Monzote, L.; Sharifi-Rad, J.; Ezzat, S.M.; Salem, M.A.; Merghany, R.M.; El Mahdy, N.M.; Kllç, C.S.; Sytar, O.; et al. Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health. ACS Omega 2020, 5, 11849–11872.
30. Xu, D.; Hu, M.-J.; Wang, Y.-Q.; Cui, Y.-L. Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules 2019, 24, 1123.
31. Tsiailanis, A.D.; Renziehausen, A.; Kiriakidi, S.; Vrettos, E.I.; Markopoulos, G.S.; Sayyad, N.; Hirmiz, B.; Aguilar, M.-I.; Del Borgo, M.P.; Kolettas, E.; et al. Enhancement of Glioblastoma Multiforme Therapy through a Novel Quercetin-Losartan Hybrid. Free Radic. Biol. Med. 2020, 160, 391–402.
32. Ulusoy, H.G.; Sanlier, N. A Minireview of Quercetin: From Its Metabolism to Possible Mechanisms of Its Biological Activities. Crit. Rev. Food Sci. Nutr. 2020, 60, 3290–3303.
33. Maroto, J.Á.M. Synergic Polyphenol Combination ES2391211B1. ES2391211B1, 2 October 2013.
34. De, P.; Bedos-Belval, F.; Vanucci-Bacque, C.; Baltas, M. Cinnamic Acid Derivatives in Tuberculosis, Malaria and Cardiovascular Diseases—A Review. Curr. Org. Chem. 2012, 16, 747–768.
35. Ivanov, V.; Ivanova, S.; Roomi, W.; Niedzwicki, A.; Rath, M. Novel Composition and Method for the Treatment of Hypertension. US2004242504A1, 30 May 2003.
36. Jalili, T. Quercetin Supplementation to Treat Hypertenstion. US2004258674A1, 12 April 2004.
37. Larson, A.J.; Symons, J.D.; Jalili, T. Quercetin: A Treatment for Hypertension?—A Review of Efficacy and Mechanisms. Pharmaceuticals 2010, 3, 237–250.
38. George, B.P.; Parimelazhagan, T.; Sajeesh, T.; Saravanan, S. Antitumor and Wound Healing Properties of Rubus Niveus Thunb. Root. J. Environ. Pathol. Toxicol. Oncol. 2014, 33, 145–158.
39. Polera, N.; Badolato, M.; Perri, F.; Carullo, G.; Aiello, F. Quercetin and Its Natural Sources in Wound Healing Management. Curr. Med. Chem. 2019, 26, 5825–5848.
40. Ezzat, S.M.; Choucry, M.A.; Kandil, Z.A. Antibacterial, Antioxidant, and Topical Anti-Inflammatory Activities of Bergia Ammannioides: A Wound-Healing Plant. Pharm. Biol. 2016, 54, 215–224.
41. Pastorino, G.; Marchetti, C.; Borghesi, B.; Cornara, L.; Ribulla, S.; Burlando, B. Biological Activities of the Legume Crops Melilotus Officinalis and Lespedeza Capitata for Skin Care and Pharmaceutical Applications. Ind. Crops Prod. 2017, 96, 158–164.
42. Lodhi, S.; Jain, A.; Jain, A.P.; Pawar, R.S.; Singhai, A.K. Effects of Flavonoids from Martynia Annua and Tephrosia Purpurea on Cutaneous Wound Healing. Avicenna J. Phytomed. 2016, 6, 578–591.

43. Tang, J.; Diao, P.; Shu, X.; Li, L.; Xiong, L. Quercetin and Quercitrin Attenuates the Inflammatory Response and Oxidative Stress in LPS-Induced RAW264.7 Cells: In Vitro Assessment and a Theoretical Model. BioMed Res. Int. 2019, 2019, 7039802.
44. Wei, B.; Zhang, Y.; Tang, L.; Ji, Y.; Yan, C.; Zhang, X. Protective Effects of Quercetin against Inflammation and Oxidative Stress in a Rabbit Model of Knee Osteoarthritis. Drug Dev. Res. 2019, 80, 360–367.
45. Sul, O.-J.; Ra, S.W. Quercetin Prevents LPS-Induced Oxidative Stress and Inflammation by Modulating NOX2/ROS/NF-KB in Lung Epithelial Cells. Molecules 2021, 26, 6949.
46. Nakamura, M.; Fukuma, Y.; Notsu, K.; Kono, M. Quercetin and HSC70 Coregulate the Anti-Inflammatory Action of the Ubiquitin-like Protein MNSFβ. Mol. Biol. Rep. 2022, 49, 1213–1222.
47. Chen, T.; Zhang, X.; Zhu, G.; Liu, H.; Chen, J.; Wang, Y.; He, X. Quercetin Inhibits TNF-α Induced HUVECs Apoptosis and Inflammation via Downregulating NF-KB and AP-1 Signaling Pathway in vitro. Medicine 2020, 99, e22241.
48. Ma, J.-Q.; Li, Z.; Xie, W.-R.; Liu, C.-M.; Liu, S.-S. Quercetin Protects Mouse Liver against CCl4-Induced Inflammation by the TLR2/4 and MAPK/NF-KB Pathway. Int. Immunopharmacol. 2015, 28, 531–539.
49. Bairwa, R.; Kakwani, M.; Tawari, N.R.; Lalchandani, J.; Ray, M.K.; Rajan, M.G.R.; Degani, M.S. Novel Molecular Hybrids of Cinnamic Acids and Guanylhydrazones as Potential Antitubercular Agents. Bioorg. Med. Chem. Lett. 2010, 20, 1623–1625.
50. Sotgiu, G.; Centis, R.; D'Ambrosio, L.; Tadolini, M.; Castiglia, P.; Migliori, G.B. Do We Need a New Fleming Époque: The Nightmare of Drug-Resistant Tuberculosis. Int. J. Mycobacteriol. 2013, 2, 123–125.
51. Sasikumar, K.; Ghosh, A.R.; Dusthackeer, A. Antimycobacterial Potentials of Quercetin and Rutin against Mycobacterium Tuberculosis H37Rv. 3 Biotech 2018, 8, 1–6.
52. Huang, S.; Czech, M.P. The GLUT4 Glucose Transporter. Cell Metab. 2007, 5, 237–252.
53. Dhanya, R. Quercetin for Managing Type 2 Diabetes and Its Complications, an Insight into Multitarget Therapy. Biomed. Pharmacother. 2022, 146, 112560.
54. Ahrens, M.J.; Thompson, D.L.; Atm Metabolics Lllp. Composition for Treating Diabetes and Metabolic Disorders with Quercetin, Myrcetin and Chlorogenic Acid. EP2129371B1, 11 March 2008.
55. Kruthiventi, A.; Javed, I. Pharmaceutical Co-Crystals of Quercetin. US20120258170A1, 30 October 2009.
56. Ansari, P.; Choudhury, S.T.; Seidel, V.; Rahman, A.B.; Aziz, M.A.; Richi, A.E.; Rahman, A.; Jafrin, U.H.; Hannan, J.M.A.; Abdel-Wahab, Y.H.A. Therapeutic Potential of Quercetin in the

Management of Type-2 Diabetes Mellitus. Life 2022, 12, 1146.

57. Ali, A.H.; Sudi, S.; Shi-Jing, N.; Rozianoor, W.; Hassan, M.; Basir, R.; Agustar, H.K.; Embi, N.; Sidek, H.M.; Latip, J. Dual Anti-Malarial and GSK3 β-Mediated Cytokine-Modulating Activities of Quercetin Are Requisite of Its Potential as a Plant-Derived Therapeutic in Malaria. Pharmaceuticals 2021, 14, 248.
58. da Silva, A.A.; Maia, P.I.d.S.; Lopes, C.D.; de Albuquerque, S.; Valle, M.S. Synthesis, Characterization and Antichagasic Evaluation of Thiosemicarbazones Prepared from Chalcones and Dibenzalacetones. J. Mol. Struct. 2021, 1232, 130014.
59. Tasdemir, D.; Kaiser, M.; Brun, R.; Yardley, V.; Schmidt, T.J.; Tosun, F.; Ru, P. Antitrypanosomal and Antileishmanial Activities of Flavonoids and Their Analogues: In Vitro, In Vivo, Structure-Activity Relationship, and Quantitative Structure-Activity Relationship Studies. Antimicrob. Agents Chemother. 2006, 50, 1352–1364.
60. Fábio, M.; Rocha, G.; Sales, J.A.; Gleiciane, M.; Galdino, L.M.; Aguiar, L.D.; Pereira-Neto, W.D.A.; Cordeiro, R.D.A.; Souza, D.D.; Maia, C. Antifungal Effects of the Flavonoids Kaempferol and Quercetin: A Possible Alternative for the Control of Fungal Biofilms. Biofouling 2019, 35, 320–328.
61. Tebbi, C.K. Sickle Cell Disease: A Review. Hemato 2022, 3, 341–366.
62. Lozano, R.; Azarang, A.; Wilaisakditipakorn, T.; Hagerman, R.J. Fragile X Syndrome: A Review of Clinical Management. Intractable Rare Dis. Res. 2016, 5, 145–157.
63. Chodoeva, R. Quercetin-Based Composition for Treating Rhinosinusitis. US2021000787A1, 15 February 2021.
64. Tiboc-Schnell, C.N.; Filip, G.A.; Man, S.C.; Decea, N.; Moldovan, R.; Opris, R.; Sas, V.; Tabaran, F. Quercetin Attenuates Naso-Sinusal Inflammation and Inflammatory Response in Lungs and Brain on an Experimental Model of Acute Rhinosinusitis in Rats. J. Physiol. Pharmacol. 2020, 71, 479–490.
65. Zahedipour, F.; Kesharwani, P.; Sahebkar, A. Mechanisms of Multidrug Resistance in Cancer. In Aptamers Engineered Nanocarriers for Cancer Therapy; Elsevier: Amsterdam, The Netherlands, 2022; pp. 51–83.
66. Joshi, N.S.; Aggarwal, P.; Hiprara, V.K.; Jaggi, M.; Singh, A.; Awasthi, A.; Verma, R. Novel Quercetin Derivatives as Anti-Cancer Agents. US2011034413A1, 8 August 2008.
67. Otsuka, Y.; Egawa, K.; Kanzaki, N.; Izumo, T.; Rogi, T.; Shibata, H. Quercetin Glycosides Prevent Dexamethasone-Induced Muscle Atrophy in Mice. Biochem. Biophys. Rep. 2019, 18, 100618.
68. Karaboga, A.S.; Perez-Neuno, V.I.; Souchet, M.; Decaudin, D. Muscle Atrophy Inhibitor Containing Quercetin Glycoside. CN106255500A, 2 April 2015.

Retrieved from https://encyclopedia.pub/entry/history/show/119560